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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,187	07/30/2003	Jurgen Engel	103832-477-NP	9817

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
07/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/632,187	ENGEL ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/21/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed on **7/12/07** presents remarks and arguments to the office action mailed on **2/12/07**. Applicant's request for reconsideration of the rejection of claims in the last office action has been considered.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of Claims

Claims 1-5, and 7-12 are pending in this office action. Claims 1-3, 5-6, 8-9 and 11-12 are currently amended.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Nowhere in the specification or claim is the term "excluding cyclophophamide" disclosed or taught as recited.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-5 and 7-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter (prodrugs) which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

the quantity of experimentation necessary

Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

the presence or absence of working examples

There is no direction in the specification concerning produgs; there are no working examples for a prodrug of a compound of formula II.

The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body., e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be

undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph, the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modem Pharmaceutics) Banker, G.S. et al, "Modem Pharmaceutics, 3ed.",Marcel Dekker, New York, 1996, pages 451 and 596. The first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug, f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making of prodrugs as a collaborative team of synthetic pharmaceutical Chemists and metabolism experts. All would have a Ph.D. degree and several years of industrial experience.

The breadth of the claims includes numerous of the hundreds of thousands of compounds of formula II.

Undue experimentation will be required to determine if any particular alkylphosphocholine is, in fact, a prodrug.

Nowhere in the specification or claims are directions given for preparing the "prodrugs" of the claimed compound. Since the structures of these "prodrugs" are uncertain, direction for their preparation must and metabolism experts of how to search for a “prodrug” hardly constitute instructions of how to make such a compound.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim 7 is broad and generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of antitumor inhibitors of signal transduction in the form of high and low molecular weight inhibitors of receptors and or cystosolic kinases. The specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of antitumor inhibitors of signal

transduction in the form of high and low molecular weight inhibitors of receptors and or cystosolic kinases.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

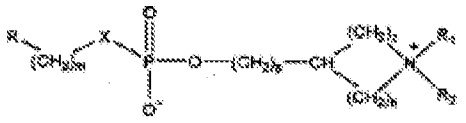
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

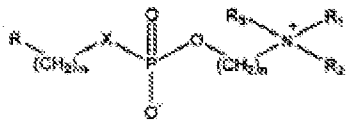
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hilgard et al. Cancer Chemother. Pharmcol. (1993) 32: 90-95 in view of Goodman and Gilman (already of record)

The claims recite a method of treating mammary carcinoma comprising administering an alkylphosphocholine of formulae



Formula II and



Formula I in combination with an approved antitumor agent e.g. carboplatinum, oxaliplatinum etc, wherein the alkylphosphocholine is administered before or prior to the approved antitumor agent.

Hilgard et al, teach the use of alkylphosphocholine compound which is (embraced by the above formulae, see page 91, left col.) combined with a conventional platinum complex for the treatment of mammary induced carcinoma, see page 93, left col. bridging right col.

The Hilgard reference fails to teach the specific antitumor compounds (oxaliplatinum carboplatinum, bleomycin etc) and the administration of alkylphosphocholine prior or during the treatment.

It is for this reason that Goodman and Gilman is introduced.

Goodman and Gilman teach adjuvant therapy is commonly used in breast cancer patients. See page 1226, last line and page 1230 lines 1-2. Further the reference teaches classes of antineoplastic agents used for the treatment of specific disease. For example, 5-FU, methotrexate, doxorubicin, vinblastine are known to be useful for the treatment of breast cancer.

One of ordinary skill in the art would have been motivated to combine the cited references of Hilgard with Goodman and Gilman for the treatment of breast/mammary cancer with the claimed compounds above and substitute the cisplatinum with carboplatinum or oxaliplatinum because the Hilgard reference teaches that compounds of formulae I and II have been combined with cisplatinum. Cisplatinum is a platinum based drug and substituting one for another, would have been within the purview of the skilled artisan because since cisplatinum, carboplatinum and oxaliplatinum are from the same family of compounds, one would expect the same result as with cisplatinum. Also the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205

USPQ 1069 (CCPA 1980), wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant method claims, given the teaching of the prior art methods of using an alkylphosphocholine and a chemotherapeutic agent individually for treating breast/mammary carcinoma, it would have been obvious to use both compounds for the treatment of breast/mammary carcinoma because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as therapeutic agents. And the combination of such has already been taught as discussed above. Further combinations of drugs are used for therapeutic advantages they provide over the use over single agents.

As to the administration of prior to or during the administration of compounds of formulae I and II, this also is within the purview of the skilled artisan. Adjuvant therapy is always given either prior, in combination or after administration of one of the drugs a well known practiced known in the art of medicine (absent factual evidence). Nothing is seen as unobvious in the administration mode. Also the motivation to can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results for their common known purpose. Section MPEP 2144.07.

II. Claims 1-5 and 7-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hilgard[1] et al. Cancer Chemother. Pharmacol. (1993) 32: 90-95) (of record) in view of Goodman and Gilman (of record) as applied to claims 1-3 and further in view of Hilgard[2] et al (item No. 5 of IDS submitted 11/28/03) and further in view of Princlpe et al. Anti-Cancer Drugs 1992 3, 577-587 (Applicants IDS submitted 5/21/08).

Claims 5, 9, 11 and 12 are obvious variations of claims 1-3 as applied supra.

Hilgard[1] and Goodman and Gilman are applied her as above. The combined references failed to teach the compound D21266 (which is the octadecyl 1,1-dimethylpiperiddinium-4-yl phosphate). For this reason Hilgard et al. is introduced.

Hilgard[2] et al. teach D-21266 in combination with antitumor agents such as adriamycin cyclophosphamide and cisplatin very well known antineoplastic agents in the art of oncology. See pages 157, last paragraph and 163 para. 2 and 3.

Princlpe et al. teach combination of ether phospholipids with various antineoplastic agents such as adriamycin, bleomycin, methotrexate, vinblastine in the treatment of cancer, see page 578, under chemical compounds.

One of ordinary skill in the art would have been motivated to combine the cited references, employ the teachings by Goodman and Gilman in choosing the appropriate antineoplastic agent that are signal transduction and are monoclonal antibodies as in claims 5 and 7-8. One of ordinary skill in the art would have been motivated to combine all the cited references and administer an adjuvant therapy of the alkylphospholipid with anticancer agent because the cited references Hilgard[1], Hilgard[2] and Princlpe teach the use of antineoplastic agents with the drug. Also based on the disease, these

antineoplastic agents can be combined to treat a specific disease as taught by Goodman and Gilman.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Withdrawn Claim Rejections - 35 USC § 103

Claims 2, 7 and 10 rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al., 6,093,704, and Nickel et al., 6,696,428, and Nössner et al., 6,172,050 (all references already of record) in view of Calabresi et al., Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition as evident by Kasianenko 1998:87. (2pages) Abstract only. Applicant's arguments with respect to claims 2, 7 and 10 have been considered but are moot in view of the new ground(s) of rejection given above.

Maintained

Claims 2, 7 and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hilgard et al., Cancer Chemother. Pharmcol., (1993) 32: 90-95 in view of Stekar et al., European J. of Cancer, Vol. 31(3), pp. 372-374, 1995 (Applicant submitted ref.).

Applicant argues that both Hilgard and Stekar references disclose the use of miltefosin in combination with cyclophosphamide and cisplatin but fails to teach any other combinations.

This however, is found not persuasive because Hilgard teaches the combination of miltefosin with cisplatin showed considerable therapeutic synergy. This showing is within the claim limitation wherein a combination of miltefosin with cisplatin is used. Cisplatin is a platinum based drug, one of ordinary skill in the art would expect the same type of success seen with cisplatin if cisplatin is substituted oxaliplatinum, carboplatinum because these antineoplastic drugs are platinum based and are in the same family with cisplatinum. Thus amending the claims to be free of cisplatinum does not render the claims free of the rejection. As to the cancellation of cyclophosphamide, it would have been obvious since Stekar teaches a combination of the drug miltefosin and Hilgard teaches a combination with cisplatinum, one of ordinary skill in the art would have been motivated to substitute cis-platinum with a platinum based chemotherapeutic agent in combination with miltefosin. As to the argument that the combine use might lead to synergistically enhanced detrimental side effects is not claimed, the claim only calls for a combination of agents miltefosin and an antitumor substance, whether they cause enhance detrimental side effects is not read into the claims nor is the mechanism

of action of the alkylphosphocholine. Based on the above discussion, the rejection is maintained as in the last office action of record.

Applicant's amendment did not overcome the rejected claims.

Claims 1-5 and 7-12 rejected under 35 U.S.C. 103(a) as being unpatentable over Hilgard et al. Cancer Chemother. Pharmcol. (1993) 32: 90-95 taken with Stekar et al. European J. of Cancer Vol. 31(3) pp 372-374, 1995 in view of Nössner et al. US 6,172,050 further in view of Patel et al., Cancer research 62, 1401-1409, March 1, 2002 is withdrawn. Applicant's arguments with respect to claims 1-5 and 7-12 have been considered but are moot in view of the new ground(s) of rejection above.

.No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/SVG/
7/08/08